REMARKS

Claims 1, 5-7, 9-10, 13-15, 17-18 and 20-21 are presently pending in this Application. In the instant Amendment, Claims 1, 5-7, 9-10, 13-15, 17-18 and 20-21 have been canceled, without prejudice, and New Claims 24-37 have been added. Support for new Claims 24-37 can be found throughout the instant Application, and particularly on pages 2 and 3 as well as in Claims 1-22 as originally filed.

Preliminary Amendment not included in Subsequent Amendments

On December 16, 2003, a Preliminary Amendment for the above-identified Application was filed with the United States Patent and Trademark Office. Unfortunately, the amendments made in the Preliminary Amendment were not carried through to subsequent amendments filed in this matter, and neither the attorneys who prepared and filed those subsequent amendments nor the United States Patent and Trademark Office, which examined those subsequent amendments, noticed the subsequent amendments omitted the amendments made in the Preliminary Amendment. The omission of the amendments made in the Preliminary Amendment in those subsequent amendments was clearly an error and done without deceptive intent.

In order to clarify the record in this matter, the instant Amendment cancels pending Claims 1, 5-7, 9-10, 13-15, 17-18 and 20-21, without prejudice, and introduces new Claims 24-37, which have no relationship with the Claims amended in the Preliminary Amendment of December 16, 2003. The undersigned apologizes to the Examiner for any inconvenience regarding this matter.

The Invention is Definite

Claims 1, 5-7, 9, 10, 13-15, 17, 20 and 21 are newly rejected under 35 U.S.C. § 112,

second paragraph as being indefinite. The Examiner has asserted that Claim 1, step a, line 3 is drawn to "a detectable change of the phenotype." It is the Examiner's position the phrase "the phenotype" lacks antecedent basis. The Examiner further notes that Claims 5-7, 9, 10, 13-15, 17 20, and 21 depend upon Claim 1 and are included in the rejection.

This rejection is respectfully traversed. Initially, it is respectfully submitted that in the instant Amendment, Claims 1, 5-7, 9, 10, 13-15, 17, 20 and 21 have been canceled, without prejudice. Hence the rejection of these Claims is MOOT. It is further respectfully submitted that new Claims 24-37 are also clearly definite. In particular, new Claim 24 is directed towards, *inter alia*, "[a] method for generating a genetically modified yeast organism for drug screening, which comprises the steps of: a) causing heterologous expression of at least one protein or protein fragment by genetic modification by introducing a foreign gene into a yeast organism ***having a phenotype***...(emphasis added)." Clearly the phrase "a detectable change of the phenotype" has proper antecedent basis in this Claim. Hence, this rejection is not applicable to new Claims 24 and 35 as well as new Claims dependent, and this rejection should be withdrawn.

The Invention is Novel

Claims 1, 9-10, 17-18 and 20-21 have been rejected under 35 U.S.C. § 102(b) as being anticipated by the teachings of Chattopadhyay *et al.* (2000, Journal of Bacteriology, 182:6418-6423) for reasons of record, April 10, 2007; January 4, 2008; and August 12, 2008. The Examiner has further asserted that arguments filed July 7, 2008 to overcome this rejection have been fully considered, but in the Examiner's opinion, are not persuasive. The Examiner contends that previously, it was argued that Chattopadhyay *et al.* do not teach all of the steps of Claim 1

because there is no teaching or suggestion of Claim 1 in Chattopadhyay *et al.*, and that Chattopadhyay *et al.* merely speculate that "...perhaps altered gene expression and modified vacuolar biochemistry contribute, at least in part, to maintaining a balanced cytosolic pH and maintaining cytosolic and vacuolar pH is important". According to the Examiner, it was further argued that Chattopadhyay *et al.* explain "[c]learly, this study has not completely addressed how btn1-Δ, with btn2-Δ and hsp30-Δ mutations, balances vacuolar pH (emphasis added)." The Examiner also believes it was previously argued that Chattopadhyay *et al.* have no teachings that a genetically modified yeast organism is caused to express heterologously at least one protein or protein fragment by genetic modification by introducing a foreign gene into the yeast, wherein the expression does not produce a detectable change in the phenotype perceptible from the outside of the yeast organism.

The Examiner though has asserted these previously made arguments are not persuasive. In making this assertion, the Examiner relies on page 18 of an office action issued April 10, 2007, where it is indicated that Chattopadhyay *et al.* teach that the BTN1 gene was disrupted in yeast, *S. cerevisiae* ("btn1-Δ"), and that no phenotype was seen in these yeast. The Examiner further believes that DNA microarray results of btn1-Δ yeast indicate that two genes, HSP30 and BTN2, were unregulated, and that Chattopadhyay *et al.* teach that yeast comprising deletions of HSP30, BTN1, and BTN2 exhibited diminished growth at low pH (Chattopadhyay *et al.*, page 6418, 2nd col., 2nd paragraph, see also page 6420, 1st col.).

With regard to previous indications that "...perhaps altered gene expression and modified vacuolar biochemistry contribute, at least in part, to maintaining a balanced cytosolic pH and

maintaining cytosolic and vacuolar pH is important" and that "[c]learly, this study has not completely addressed how btn1-Δ, with btn2-Δ and hsp30-Δ mutations, balances vacuolar pH," the Examiner contends these citations do not address the 102 rejection at hand because, in the Examiner's opinion, regardless of Chattopadhyay *et al.*'s interpretation of their data, the Examiner believes Chattopadhyay *et al.* teach the steps of Claim 1. Thus, it is the Examiner's position Chattopadhyay *et al.* anticipate the Claims. The Examiner also notes that the rejection of Claim 23 is withdrawn as the Claim has been canceled.

This rejection is respectfully traversed. In the instant amendment, 1, 9-10, 17-18 and 20-21 have been canceled, without prejudice. Hence, the rejection of these Claims is MOOT. It is further respectfully submitted that new Claim 24 as well as new Claims dependent thereto are clearly novel in light of the teachings of Chattopadhyay *et al.* New Claim 24 is directed towards, *inter alia*, a method for generating a genetically modified yeast organism for drug screening, which comprises the steps of: a) ***causing heterologous expression of at least one protein or protein fragment by genetic modification by introducing a foreign gene into a yeast organism having a phenotype.*** Thus, it is clear from new Claim 24 that in a method of the instant Invention, a "foreign gene" is introduced a yeast organism, and that "foreign gene" is heterologously expressed to produce the at least one protein or protein fragment. Yet, Chattopadhyay *et al.* teach ***nothing*** with respect to introducing a ***foreign gene*** that is heterologously expressed to produce at least one protein or protein fragment the encoded by a foreign gene. Quite the contrary, Chattopadhyay *et al.* clearly teach ***deleting endogenous genes*** from the yeast. Indeed, on page 6421, Chattopadhyay *et al.* clearly state:

> In this study, we demonstrate that ***deletion*** of either or both of the two genes HSP30 and BTN2, which have increased expression in *btn1*-Δ strains, did not alter the pH-dependent resistance to ANP in *btn1*-Δ strains nor did it result in resistance to ANP for *BTN1*$^+$ strains. Furthermore, the *btn1*-Δ *hsp2*-Δ *btn2*-Δ strain, with all three genes deleted, is viable and shows no growth defect under normal conditions (results not presented).

(Emphasis added).

It is acknowledged that Chattopadhyay *et al.* inserted genes into the strains used in their experiments. However, there is no evidence these genes were expressed. Rather, Chattopadhyay *et al.* report these genes were inserted into endogenous genes to ***disrupt*** the expression of those endogenous genes. In the Materials and Methods section on page 6419, Chattopadhyay *et al.* make clear that:

> Deletion of *BTN1* has been described previously (22). Deletion of *HSP30* and *BTN2* was performed by standard techniques. *HSP30* was ***disrupted*** using the plasmid pSPHSP30 obtained from P. Piper (University College London). Briefly, a 1.1-kb *Hin*dIII fragment, containing the *URA3* gene inserted in the *Hin*dIII site in the coding region of *HSP30*, was used for ***disruption*** of *HSP30* by homologous recombination. *BTN2* was ***disrupted*** with the plasmid pAB2197 containing a 1.1-kb *Hin*dIII fragment with the *URA3* gene blunt ended and ligated in the *Nde*I site of the coding region of *BTN2*.

(Emphasis added.)

Thus, in Chattopadhyay *et al.*, the *URA3* gene was inserted, but no evidence was presented it was ever heterologously expressed.

MPEP § 706.02 specifically states that "...for anticipation under 35 U.S.C. 102, ***the reference must teach every aspect of the claimed invention*** either explicitly or impliedly. Any feature not directly taught must be inherently present (emphasis added)." Since new Claim 24 is

directed towards, *inter alia*, a method for generating a genetically modified yeast organism for drug screening, which comprises the steps of: a) causing heterologous expression of at least one protein or protein fragment by genetic modification by introducing a foreign gene into a yeast organism having a phenotype, and Chattopadhyay *et al.* teach the ***deletion*** of endogenous genes and the insertion of a gene that does not undergo heterologous expression, ***it is impossible*** that Chattopadhyay *et al.* teach every aspect of the claimed Invention, either explicitly or impliedly. Hence, the teachings of Chattopadhyay *et al.* clearly ***do not*** anticipate new Claim 24 and new Claims dependent thereto.

The Invention is Nonobvious

Claims 1, 5-7 and 13 have been newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Chattopadhyay *et al.* (2000, Journal of Bacteriology, 182;6418-6423) in view of Sauer (1987, Molecular and Cellular Biology, 7:2087-2096). The Examiner has asserted that Chattopadhyay *et al.* teach a method of generating genetically modified yeast comprising the steps of disrupting BTN1, conducting a microarray study to determine that HSP30 and BTN2 were upregulated, and disrupting HSP30 and BTN2 expression in BTN1 null yeast. However, the Examiner has admitted Chattopadhyay *et al.* do not teach that that the modified expression step is inducible.

The Examiner has further asserted that at the time of filing, Sauer teaches that the cre-lox site-specific recombination system was shown to function in an efficient manner in yeast. The Examiner believes the cre gene, which codes for a site-specific recombinase, was placed under control of the yeast GAL1 promoter, and lox sites flanking the LEU2 were integrated into two different chromosomes in both orientations. The Examiner also believes Sauer teaches excise

recombination at the lox sites (as measured by the loss of the LEU2 gene) was promoted efficiently by the Cre protein and was dependent upon induction by galactose (Sauer, abstract).

In light of the Examiner's interpretations of the teachings of Chattopadhyay *et al.* and Sauer, the Examiner believes it would have been obvious to take the cre-lox system taught by Sauer and to flank the endogenous BTN1 sequence with lox sites. The Examiner contends an artisan would have done so in order to arrive at a yeast culture that can be split in half, wherein one half is induced with galactose. The Examiner has also asserted an artisan would then purify the mRNA from the galactose-induced and uninduced yeast and compare the mRNA expression between them in order to determine what genes were up- and down regulated following loss of BTN1 expression.

It is also the Examiner's position that, with regard to the Claims being drawn to the knockout of the differentially expressed gene is carried out by replacing at least part of the coding sequence of the differentially regulated gene with the coding sequence of a reporter gene or parts of the reporter gene sequence (Claim 13), the Examiner believes Chattopadhyay *et al.* teach that to make the HSP30 and BTN2 knockout, part of the coding region for both genes was replaced by a URA3 gene (Chattopadhyay *et al.*, page 6419, 1st col. Under "Yeast Strains, growth and plasmids").

This rejection is respectfully traversed. Initially, it is respectfully submitted that in the instant Amendment, Claims 1, 5-7 and 13 have been canceled, without prejudice. Hence, this rejection of Claims 1, 5-7 and 13 is MOOT. It further respectfully submitted that new Claims 24 and 35 as well as Claims dependent thereto are patentable in light of the teachings of Chattopadhyay *et al.* in view of Sauer.

In making this rejection, the Examiner has admitted that Chattopadhyay *et al.* do not teach that the modified expression step is inducible. The Examiner then looks to the teachings of Sauer to develop an inducible yeast strain of the instant Invention. The Examiner believes the teachings of Sauer would suggest to or motivate one of ordinary skill in the art to flank the BTN1 sequence with lox sites. However, this suggestion still does not result in "[a] method for generating a genetically modified yeast organism for drug screening, which comprises the steps of: a) ***causing heterologous expression of at least one protein or protein fragment by genetic modification by introducing a foreign gene into a yeast organism having a phenotype....***" (See new Claim 24 above). It is respectfully submitted that the combination of the teachings of Sauer to create an inducible strain with the teachings of Chattopadhyay *et al.* does not result in the instant Invention. Thus, contrary to the Examiner's assertions, no motivation or suggestion exists to combine the references cited in this rejection as the Examiner has done. Rather, it is respectfully submitted the instant Disclosure provided the Examiner with the motivation to combine these references in an unsuccessful attempt to reconstruct the instant Invention. However, the Examiner cannot rely on impermissible hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Feil.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). Hence, this rejection should be withdrawn.

Furthermore, Claims 1, 9-10, 14-15, and 17-21 have been newly rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi *et al.* (2000, FEBS Letters, 470:156-160). The Examiner has asserted DeRisi *et al.* teach that PDr1p/Pdr3p transcription factors render the cell resistant to chemical and nutritional stress in several ways other than the well-known regulation of ABC efflux transporters. It is the Examiner's belief that after overexpressing Pdr1p and/or Pdr3p in *S. cerevisiae* and identifying upregulated and downregulated genes, DeRisi *et al.* teach that many of the genes overexpressed by the PDR1-3 and PDR3-7 mutations encode proteins that reduce intracellular accumulation of hydrophobic compounds, modulate enzymes involved in lipid synthesis and cell wall metabolism. It is further the Examiner's position that DeRisi *et al.* teach that it would be interesting to investigate whether similar strategies for defense against noxious chemical agents are employed by other microorganisms, such as pathogenic yeasts (DeRisi *et al.*, abstract and page 159, 2nd col., 3rd paragraph).

In making this rejection though, the Examiner has admitted DeRisi *et al.* do not specifically teach that the upregulated genes in yeast overexpressing Pdr1p and/or Pdr3p were knocked out or that the downregulated genes were not overexpressed. Yet, the Examiner believes it would have been obvious for an artisan to knockout the upregulated genes and overexpress the downregulated genes in Pdr1p, Pdr3p or Pdr1p/Pdr3p yeast, such that an artisan would eliminate yeast that are resistant to chemical and nutritional stress. The Examiner further believes an artisan would have carried out the method in *S. cerevisiae* and adapted the treatment to pathogenic yeast.

With regard to the Claims being drawn to the yeast not exhibiting a detectable change in phenotype (claim 1, step a), the Examiner has asserted the yeast taught by DeRisi *et al.* do not

have a detectable phenotype as the Examiner believes the morphology of the yeast is not unaffected. In addition, the Examiner contends DeRisi *et al.* can be interpreted to exhibit no detectable phenotype on the behavior of the organism when the detectable phenotype is defined to be rate of proliferation. However, the Examiner has admitted the rate of proliferation would be affected in Pdr1p and/or Pdr3p yeast that comprise a deletion in an upregulated gene or in yeast that comprise a construct overexpressing a downregulated gene as the upregulated genes are drawn to genes involved in drug resistance (DeRisi *et al.*, page 158). Furthermore, the Examiner has asserted that genes that are downregulated are drawn to genes involved in transport of acids (DeRisi *et al.*, page 159), which would affect the homeostasis of the yeast.

This rejection is respectfully traversed. In the instant Amendment, Claims 1, 9-10, 14-15, and 17-21 have been canceled, without prejudice. Hence, this rejection of Claims 1, 9-10, 14-15, and 17-21 is MOOT.

It is further respectfully submitted that new Claim 24 as well as new Claims dependent thereto are clearly patentable over the teachings of DeRisi *et al.* DeRisi *et al.* teach that inserting in *S. cerevisiae* mutated ***endogenous genes*** that encode mutated endogenous proteins *PDR1-3* and *PDR3-7* of *S. cerevisiae* results in changes in the transcript level by more than two fold, positively or negatively, for 49 genes of *S. cerevisiae*. *Id.* at 159. The fact remains though that the mutated genes are ***endogenous*** to *S. cerevisiae*. Indeed, DeRisi *et al.* specifically state:

> One of the most important powerful pleiotropic drug resistance mutations is *PDR1-3*, derived from a [*S. cerevisiae*] strain originally isolated by Guérineau et al. [10]. This mutation dramatically increases the expression of *PDR5* mRNA [5,9,11,12], as well as that of other genes....More importantly, in the *PDR1-3* mutant, the corresponding proteins are highly overexpressed and apparently correctly trafficked to the plasma membrane in an active

> form, able to confer drug resistance and to hydrolyze nucleoside triphosphates [11, 12, 16].
>
> In addition to pdr1p, [*S. cerevisiae*] yeast contains a homologue called pdr3p [17], encoded by a gene originally identified and mapped by Subik et al. [18,19]. Pdr3p and Pdr1p share identical bonding sites on the promoters of *PDR5, SNQ2* and *YOR1* [13,14,16,20-22]. Among other mutations, *PDR3-7* markedly enhances pleiotropic drug resistance [23].

(Emphasis added).

It is respectfully submitted that despite having mutations, these two mutated genes originate from *S. cerevisiae* and thus are indeed ***endogenous genes.***

In stark contrast, new Claim 24 and Claims dependent thereto are directed towards, *inter alia*, "[a] method for generating a genetically modified yeast organism for drug screening, which comprises the steps of: a) causing heterologous expression of at least one protein or protein fragment by genetic modification by introducing a ***foreign gene*** into a yeast organism having a phenotype...(emphasis added)." Similarly, new Claim 35 is directed towards, *inter alia*, a genetically modified yeast, having a)genetically modified expression of at least one ***foreign gene***, which results in compensating differential expression of at least one other gene endogenous to the modified yeast organism yeast. It is respectfully submitted there is no teaching or suggestion in DeRisi *et al.* to insert a ***foreign gene*** into *S. cerevisiae* to undergo heterologous expression.

Moreover, DeRisi *et al.* also admit limitations in their teaching. For example, on page 159 they explain "...the pattern of PDR-regulated genes here reported ***is only valid for the reported strains under the specific growth conditions used (synthetic glucose media and early exponential growth phase*** (emphasis added)."

Consequently, since DeRisi *et al.* do not introduce a foreign gene into the strain, which is an element of new Claim 24 as well as new Claim 35, and since DeRisi *et al.* admit their method is very limited because it is only valid for the growth conditions they used, it is respectfully submitted that new Claim 24 and Claims dependent thereto, as well as new Claim 35 and Claims dependent thereto are clearly ***unobvious*** to one of ordinary skill in the art in light of the teachings of DeRisi *et al.*, and this rejection should be withdrawn.

Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

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